Interview

The undersigned wishes to thank Examiner Niland for the courtesies extended during the personal interview held for this application on October 17, 1996. Applicants arguments presented in this interview are accurately reflected in the Examiner Interview Summary Record and are further elaborated upon in the discussion below.

Rejection Under 35 U.S.C. §103

Claims 1-15 stand rejected under 35 U.S.C. §103 over Tanabe, et al., U.S. Patent No. 5,443,454 ("Tanabe"), in view of Taki, Medical Tribune, pp. 46-47, October 26, 1989 ("Taki"), Leshchiner, et al., U.S. Patent No. 4,795,741 ("Leshchiner"), Okada, et al., U.S. Patent No. 5,202,352 ("Okada"), and Winchell, U.S. Patent No. 4,079,124 ("Winchell"). For the following reasons, this rejection is traversed.

Initially, Applicants note with appreciation the indication in the Examiner Interview Summary Record that the Examiner will consider allowing the method claims of this application over arguments cited in the final Office Action which were directed to fiber spinning techniques. Accordingly, the following arguments are primarily directed to composition Claims 1-6.

Applicants' Invention

The claimed invention is directed to Applicants' discovery of novel compositions comprising an ethylene vinyl alcohol copolymer (EVOH) dissolved in a biocompatible solvent and a water insoluble contrast agent selected from either tantalum, tantalum oxide, or barium sulfate which compositions can be employed to embolize mammalian blood vessels. Accordingly, Applicants' claimed invention is directed both to a composition comprising EVOH, a biocompatible solvent and the specified water insoluble contrast agent *as well as to* methods for embolizing such blood vessels using such compositions.

When used to embolize blood vessels, the compositions of this invention are preferably delivered to the vascular site by injection or catheter delivery. Upon contact with blood at the site of delivery, the biocompatible solvent diffuses away whereupon the EVOH and water insoluble contrast agent rapidly form a coherent solid material which embolizes the blood vessel. Accordingly, when so employed, two important features of the compositions of this invention are the ability of the compositions to be delivered to the vascular site and the ability of the compositions, upon delivery, to form a coherent solid material at the vascular site.

The delivery to the vascular site of the compositions of this invention necessitates that the compositions be of sufficiently low viscosity to permit delivery, e.g., by injection or catheter, to the vascular site. Whether an embolizing composition has a low viscosity depends, in part, upon the compatibility of the components employed in the composition with incompatible components leading to compositions having a higher viscosity than compatible components. For instance, as shown in Example 4 of the specification, not all combinations of contrast agents with EVOH and DMSO[1] are compatible as evidenced by changes in the viscosity of the resulting composition. Specifically, while the addition of either 35 weight percent barium sulfate or tantalum[2] did not materially alter the viscosity of the EVOH/DMSO composition, the addition of 38.5 weight percent metrizamide more than doubled the viscosity[3]. These results indicate that metrizamide is not a compatible component in this composition whereas barium sulfate and tantalum are.

Additionally, the feature of forming a coherent solid material upon contact with the aqueous blood medium is a further important feature of this invention particularly as it

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[1] In this example, DMSO is employed as the biocompatible solvent.

[2] Water insoluble contrast agents of the claimed invention.

[3] Viscosity of the DMSO/EVOH composition prior to addition of metrizamide was approximately 60 centipoise at 20°C and, after addition, the viscosity was approximately 145 centipoise at 20°C.

relates to the ability of the composition to embolize blood vessels. Simply put, a non-coherent mass formed in the blood vessels will not provide the necessary degree of repeatable embolization to be clinically useful.

In the present case, entrapment of the water insoluble contrast agent within the polymer precipitate apparently is essential to the formation of a suitable coherent precipitate upon contact with an aqueous environment as evidenced by Example 3 of this application. Specifically, in this example, compositions of this invention were compared against similar compositions employing a water soluble contrast agent. The results of this example illustrate the quality of the precipitate formed in *in vitro* experiments by injecting into an aqueous solution a composition containing ethylene vinyl alcohol copolymer (EVOH), dimethylsulfoxide (DMSO) and either a water soluble contrast agent or a water insoluble contrast agent of this invention. In the case of the water insoluble tantalum sample, a precipitate immediately formed which was characterized by firm spongy filaments and nodules. The water soluble metrizamide sample on the other hand did not form a well defined solid mass as the metrizamide rapidly diffused away.

Analysis of Rejection

Returning back to the rejection and as noted during the interview, Applicants acknowledge that the art of record establishes a *prima facie* case of obviousness against composition Claims 1-6. However, Applicants submit that the data in this application as discussed above evidences surprising and unexpected results vis-a-vis the closest prior art which data rebuts the *prima facie* case and renders Claims 1-6 patentable. Specifically, Applicants note that the test for non-obviousness articulated by the Court of Appeals for the Federal Circuit in *In re Sernaker* is a two-part analysis based on the prior art which seeks to determine:

> (a) whether a combination of the teachings of all or any of the references would have suggested (expressly or by implication) the possibility of achieving further improvement by combining such teachings along the line of the invention in suit, and

> (b) whether the claimed invention achieved more than a combination which any or all of the prior art references suggested, expressly or by reasonable implication.

In re Sernaker, 702 F.2d at 994, 217 U.S.P.Q. 1, at 5 (Fed. Cir. 1983).

The first part of the test goes to the question of motivation, and refers to a well established holding from earlier case law that there must be some logical reason at the time of the invention for combining the references along the lines of the invention; otherwise the use of the teachings as evidence of non-obviousness will entail prohibited hindsight. *Ex parte Stauber and Eberle*, 208 U.S.P.Q. 945, 946 (Bd. App. 1980). The second part of the test covers another well-established basis for demonstrating non-obviousness--surprising and unexpected results.

Application of the test set forth by *In re Sernaker*, supra. to the references cited in the Office Action demonstrate that none of the cited references, either alone or in combination, suggest the benefits achieved by the claimed compositions and therefore these references fail to satisfy the second part of the Sernaker test.

Specifically, while the cited Tanabe reference does, in fact, recite the use of EVOH polymers in DMSO compositions for use in embolizing blood vessels, this reference only merely suggests the use of contrast agents in combination therewith without regard to the type of contrast agent. Accordingly, there is no disclosure in Tanabe of water insoluble contrast agents as per this invention nor is there any suggestion that the claimed water insoluble contrast agents would provide benefits in both the viscosity of the compositions and the quality of the precipitate formed as compared to similar compositions employing a conventional water soluble contrast agent with EVOH/DMSO as disclosed, for example, in Taki, et al.[4] In point of fact, Tanabe would suggest equivalence of both water

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[4] Taki, et al., *American Society of Neuroradiology*, 11:163-168 (1990), already of record in this application.

insoluble and water soluble contrast agents in combination with EVOH. However, the data of Examples 3 and 4 of Applicants' specification shows otherwise.

As to the cited secondary references, the cited Taki reference does not disclose the polymer composition employed in the embolization let alone the contrast agent or the solvent. The Leshchiner et al. reference teaches radio-opaque agents such as tantalum and barium sulfate *in combination with* a hyaluronan or hylan cross-linked gel. There is no teaching in Leshchiner et al. of use of these agents in combination with EVOH and Leshchiner et al. does not disclose a biocompatible solvent[5] as per this invention. Rather Leshchiner et al.'s examples use water in combination with these cross-linked gels. The Winchell reference is directed to compositions containing contrast agents which are apparently used as orally ingested compositions containing contrast agents for X-ray analysis of the upper gastrointestinal tract, but there is also disclosure of infusing the composition into a body cavity.[6] There is, however, no teaching in Winchell of using such contrast agents in combination with EVOH or DMSO. Lastly, the fact that Okada et al. disclose the surfactant properties of polyvinyl alcohol compounds is of no bearing to the claimed invention because such surfactant properties are not apparently germane to the issue of precipitation. In any event, polyvinyl alcohol is distinguished from the

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[5] The biocompatible solvent of this invention is defined at page 9 to be an organic material.

[6] The response to the first Office Action only referenced oral delivery of these compositions when, in fact, Winchell also discloses infusion by a syringe at Col. 4, lines 22-30, thereof.

copolymers of ethylene and vinyl alcohol employed in the compositions of this invention and such copolymers are not specifically disclosed by Okada.[7]

In view of the above, it is apparent that none of the cited references, either alone or in combination, suggest that the use of a specified water insoluble contrast agent in combination with EVOH and a biologically compatible solvent as per the compositions of this invention would provide for the benefits achieved in both maintaining a low viscosity and achieving a coherent precipitate as compared to a similar composition containing a water soluble contrast agent. Absent such a suggestion, the benefits achieved by the claimed compositions must be construed as surprising and unexpected.

Additionally, since the surprising and unexpected benefits of the claimed invention were achieved against the closest prior art composition, Applicants maintain that these results are probative of the patentability of the claimed compositions and rebut the *prima facie* case of obviousness against the compositions raised in the final Office Action. Specifically, as noted during the interview, the prior art teachings most germane to the invention of Claims 1-6 is found in Taki, et al., *American Society of Neuroradiology*, 11:163-168 (1990) which discloses a composition containing metrizamide (a water soluble

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[7] The compositions of this invention employ copolymers of ethylene and vinyl alcohol whereas, at Col. 7, Okada discloses the use of intravascular embolizing agents such as oils, conventional metals, insoluble salts of metals, ceramics, wax, activated carbon, natural or synthetic polymers.

The natural or synthetic polymers recited by Okada include polypeptides, polysaccharides, polyfatty acid esters, poly(amino acids), polyaldehyde, polyvinyl polymer, maleic anhydride polymer, etc. The polyvinyl polymers of Okada include copolymers such as copolymers of ethylene, propylene, butadiene, acrylic acid, acrylic acid ester, methacrylic acid, methacrylic acid ester, vinyl acetate, vinyl chloride, vinyl alcohol, vinyl pyrrolidone, vinyl ether, vinyl carbazole, styrene, styrene derivatives, α-cyanoacrylic acid ester, acrylamide, divinyl benzene, etc.

There is, however, no specific disclosure of a copolymer of ethylene and vinyl alcohol.

contrast agent), DMSO and EVOH and Applicants' comparison was made against this the most pertinent teachings of reference.

In view of the above, Applicants maintain that this rejection has been overcome by the evidence presented herein which rebuts the *prima facie* case of obviousness against the compositions raised in the final Office Action. Withdrawal of this rejection is requested.

Arguments in Final Office Action

Addressing now the arguments set forth in the final Office Action to maintain this rejection, the final Office Actions states that:

> "...It is expected that the water insoluble contrasting agent, which is a pigment in fact, would have been encapsulated by the polymer because this is well known final structural relationship of binder and pigment of pigmented binders in similar compositions such as pigmented paints and pigmented fiber spinning solutions. One only needs to examine pigmented films and fibers which existed prior to this invention to see that this is so. In such compositions of film forming polymer, solvent and pigment, the pigment is always encapsulated by the polymer and the *adhesive nature and film forming nature* of the polymer cause the pigment to be encapsulated within the polymer. The ordinary skilled artisan would have expected the same physics to occur in the instant compositions and methods, i.e., the dissolved ethylene vinyl alcohol copolymer is capable of forming film by its polymeric nature and is therefore expected to be able to coat the particles of the contrasting agent with polymer due to its low viscosity, dilute nature when dissolved, just like any other polymer solution." (emphasis added)

Applicants maintain that this logic does not withstand the evidence in this application. Specifically, the logic set forth above implicitly implicates interaction between the EVOH copolymer and the water insoluble contrast agent to explain the coherent mass formed. However, if there was substantial interaction between these components, one would reasonably expect the viscosity of an EVOH/DMSO solution to

increase significantly upon addition of the water insoluble contrast agent. Example 4 of the specification evidences that the viscosity *did not increase* upon addition of tantalum or barium sulfate to the EVOH/DMSO whereas the addition of a water soluble contrast agent, i.e., metrizamide did result in a significant increase in viscosity. Accordingly, the evidence of record demonstrates that one of ordinary skill in the art would correlate this lack of viscosity increase to little or no interaction between the polymer and the contrast agent.

Additionally, the USPTO has failed to provide any evidence that the water insoluble contrast agents of this invention would, in fact, be considered by the skill artisan as a pigment in a pigment/polymer system. Absent such evidence, Applicants take issue with this assertion.

The final Office Action further states that:

> "...The applicant argues that example 3 demonstrates unexpected results. Comparisons with water soluble contrasting agents are not persuasive because where the soluble material is in water the low amount of somewhat hydrophilic (due to the vinyl alcohol segments) polymer will be *water swellable* allowing the soluble material to dissolve into small molecules which can easily escape from the low amount of swollen binder. Where insoluble contrasting agent is used, the contrasting agent will clearly be unaffected by the water and therefore the low amount of polymer binder and any swellability of the binder would not have been expected to allow the contrasting agent to escape." (emphasis added)

The logic of this argument correlates swellability of EVOH with the conclusion as to why the skilled artisan would expect different behavior for an EVOH composition containing a water soluble contrast agent as compared to an EVOH composition containing a water insoluble contrast agent. However, this logic does not withstand the evidence in the declaration of joint inventor Michael E. Jones submitted pursuant to 37 C.F.R. §1.132

which demonstrates that when tested for swellability, EVOH (48 mol percent ethylene) did not swell upon addition to water. If EVOH does not swell in the presence of water, then the entire logic of this argument fails.

Conclusion

Applicants submit that this application is now in a condition for allowance. A notice to that effect is earnestly solicited.

Notwithstanding the above, Applicants enclose herewith a Notice of Appeal to avoid unintended abandonment of this application.

Respectfully submitted,

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